NAVAL AIR DEVELOPMENT CENTER

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Activation Energies of Acceleration and Hypoxia Stress

Bureau of Medicine and Surgery
Work Unit MR005.01.01-0121B Report No. 5

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Aerospace Medical Research Department

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SUMMARY

The activation energy of 13 kcal/M for loss of peripheral vision in man subjected to acceleration stress of +4 to +5 G_z resembles that of 12 kcal/M for survival of rats at +40 G_z, which suggests that the physiological mechanisms of acceleration protection are similar in the two species. The activation energy of survival to hypoxia stress (mouse) is 8.4 kcal/M which resembles the value of 8 kcal/M obtained for function of the normal human brain (alpha frequency of the EEG), which supports the concept that survival of the organism to hypoxia stress is indeed limited by survival of brain function. The large difference in activation energy of acceleration stress from that of hypoxia or of normal brain function suggests that tolerance to acceleration stress is not limited simply by the ability of nervous tissue to endure hypoxia, but must be dependent upon additional mechanisms.

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I. Introduction

The purpose of this paper is to present activation energy calculations for acceleration and hypoxia stress, and to show applications to determination of mechanism of survival and to choice of experimental methodology.

Activation energies have long been of importance for the study of basic physical chemistry and have been extended to biology to yield interesting correlations of enzyme reactions with integrated physiological systems[2,3]. Although activation energy seems never before to have been applied to aerospace physiology, it offers an approach totally different from those used previously and provides a new perspective.

II. Activation Energy - Its Significance and Method of Calculation

The concept of activation energy is derived originally from the absolute rate theory of chemical reactions. The rate of a chemical reaction is in general described by an equation of the form[1,2,3]

$$x = x_o e^{\frac{-E}{RT}} \qquad \text{(equation 1)}$$

where x is the rate of the chemical reaction, x_o is a quantity independent of temperature, e is the base of natural logarithms, R is the gas constant, T is absolute temperature in degrees Kelvin, and F is the activation energy of the reaction in kilocalories per mole. Theoretically, E represents the energy per mole necessary to push the reacting molecules over a barrier to the reaction. Experimentally, equation 1 is observed to describe numerous enzymatic reactions of biological systems, so that values of E for different biochemical reactions have been calculated[2,3]. It has been surmised that any specific physiological process is likely to be rate-limited by some particular slowest biochemical

process, perhaps an enzymatic reaction, which may be expected to conform to equation 1[3,4]. Hence, any physiological process is likely to conform to equation 1, so that its activation energy (E) may be calculated, and may be used to provide evidence regarding the nature of its governing enzymatic reaction. Many physiological processes have been analyzed in this way[3,5]. The distribution of activation energies of a multitude of physiological processes has been found to conform to the distribution of activation energies of a large number of enzyme reactions[3,4], which supports the above concept.

In order to decide whether the concept of activation energy is applicable to a particular physiological process, we must first have experimental data showing the dependence of the physiological process upon temperature, and second, we must test to see if the data fit equation 1. The test is done most easily if one takes logarithms of equation 1 to yield

$$\log_e x = -E/RT + \log x_o \qquad \text{(equation 2)}$$

One may then plot the experimental data in the form of the logarithm of the physiological variable ($\log_e x$) against the reciprocal of absolute temperature ($1/T$). If a straight line results, the data conform to equation 2, and hence to equation 1, which indicates that activation energy (E) may be calculated from the slope of the straight line. This test is called an Arrhenius plot, and is well known to physical chemists.

To calculate activation energy from a linear Arrhenius plot of physiological data, one may choose a nigh point and a low point from the graph, calculate $\log_e(x)$ for each of these two points, and then calculate the difference in logs, i.e. $\Delta[\log_e(x)]$, between the two points. For the same two points, one measures $1/T$, and then the difference in $1/T$ between the two points, i.e. $\Delta(1/T)$. The

activation energy of the physiological process is then calculated from the formula

$$E = \frac{2.0 \times 10^{-3} \times \Delta(\log_e x)}{\Delta(1/T)} \qquad \text{(equation 3)}$$

where E is activation energy in kilocalories per mole, i.e. calories $x10^{-3}$ per mole, x is the physiological variable in any convenient units, and T is body temperature in degrees Kelvin. E may be expressed in electron volts (ev) by division of the above value by 23.5.

III. Activation Energies of Acceleration and Hypoxia Stress and Their Significance

The mammalian response to positive (head-to-foot) acceleration stress has been separated by the work of Stiehm[6] into two distinct and different patterns. We will call these the high-G syndrome and the low-G syndrome. The two syndromes are different with respect to level and duration of the inducing acceleration, and with respect to the influence of temperature on survival, and probably have different physiological mechanisms responsible for impairment of function.

In rats, the high-G syndrome occurs at +30 G_z and above[6]. The mechanism of death seems to be cerebral hypoxia resulting in paralysis of the respiratory center of the brain[6]. Life of rats at +30 G_z and above is prolonged by cooling, presumably because oxygen consumption in brain is reduced by the low temperature[6]. In man, the black-out or unconsciousness experienced by pilots subjected to +3 to +5 G_z in planes or centrifuges has been supposed to have a similar origin in hypoxia of brain and/or retina. The lower G-tolerance of man compared to the rat is presumed to be due to the longer column of blood between heart and head in man, so that at the same G level, the human heart must pump against a much greater back pressure in order to circulate blood to the brain[6].

Let us now see what additional information can be obtained from a quantitative study of temperature effects and activation energies. First, let us note that the prolongation of life by cooling of rats at +30 G_z and above[6] has a parallel in man. In human subjects, heating decreases significantly acceleration tolerance in the +4 to +5 G_z range[7]. These findings contrast with the low-G syndrome in rats, where the opposite effect of temperature is observed[6]. Second, we shall demonstrate that the temperature effect on high-G acceleration stress is quantitatively similar in rat and man. To quantitate the temperature dependence of the response to acceleration stress, we shall calculate its activation energy, which will be compared for rat and man, and will be correlated with activation energies of other physiological processes in order to obtain information regarding mechanism.

An Arrhenius plot of rat survival to +40 G_z acceleration, using the data of Stiehm[6] yielded a linear relationship (Figure 1). An Arrhenius plot of the acceleration level for loss of peripheral vision in man exposed to positive acceleration, using the data of Burgess[7] showed a similar picture. Activation energies for acceleration stress in rat and man were computed from these plots by equation 3. The results in Table 1 show activation energies of 12 and 13 kilocalories per mole for acceleration stress in rat and man respectively. This similarity of values, despite major differences in endpoints and in other experimental conditions strongly suggests that tolerance to acceleration stress in man at +4 to +5 G_z is dependent upon the same mechanism which governs survival of the rat at +40 G_z. This is of practical importance in that it indicates that acceleration protection procedures which may be developed with relative ease and cheapness using rat experiments will probably be applicable to man.

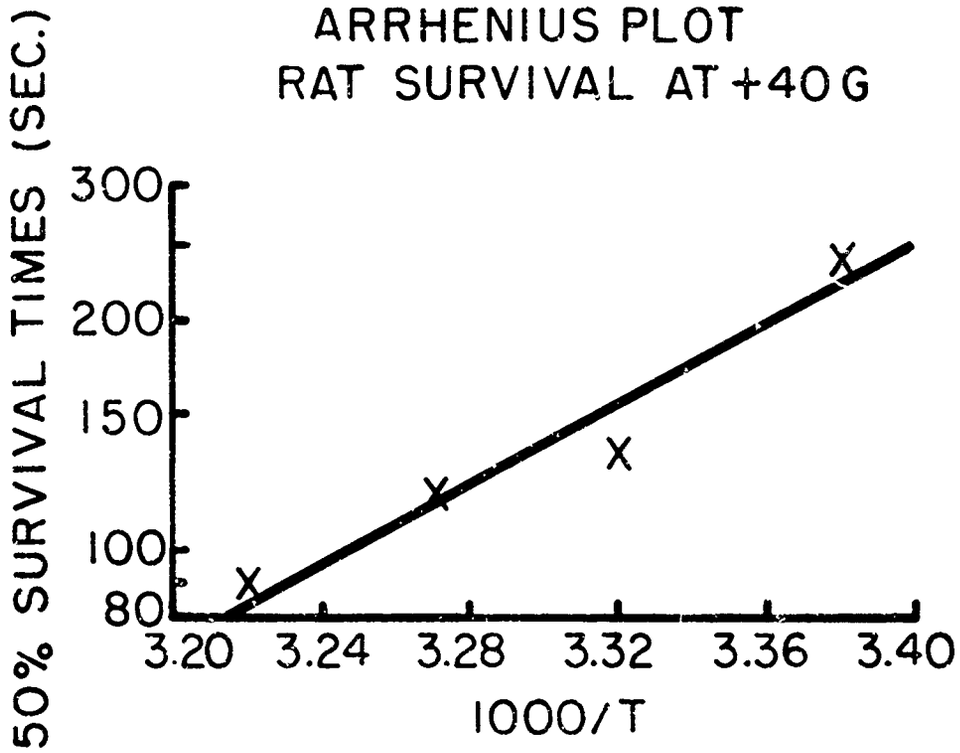

Figure 1. Arrhenius Plot of Rat Survival to Acceleration Stress of $+40G_z$. Fifty percent survival times in seconds are plotted on a log scale vs. 1000/T where T is body temperature in degrees Kelvin. Data are taken from Table 2 of Stiehm[6], which was plotted as a lognormal survival vs. time curve for each temperature, from which was estimated a 50 percent survival time for each temperature, which is plotted above.

Table 1

Activation Energies for Stresses and for Physiological Processes

Species	Stress or Process	Activation Energy
rat	acceleration (+40 G_z)	12 kcal/M
man	" (+4 to +5 G_z)	13
mouse	hypoxia	8.4 kcal/M
man	EEG (alpha rhythm) - normal brain	8 kcal/M
"	" " " moderate brain damage	11
"	" " " severe brain damage	16

Rat acceleration value was calculated from data of Figure 1. Human acceleration value was based on a similar Arrhenius plot made from data in Figure 2 of Burgess[7] on loss of peripheral vision in man as a function of air temperature, but where data has been recalculated as a function of body temperature from data of Figure 4 of Burgess[7]. Hypoxia value was obtained from an Arrhenius plot of data in Figure 1 of Madden et al[8], which represents average survival times of groups of mice subjected to hypoxia of drowning at different body temperatures. Values for EEG are those calculated by Hoagland[9] from Arrhenius plots of the frequency of the alpha rhythm as a function of body temperature in patients with brains that were normal or damaged by disease.

Let us now see what activation energies can tell us of the mechanism of acceleration stress. Let us consider first the plausible hypothesis that the limiting factor in acceleration stress is oxygen lack in the brain resulting from impaired cerebral circulation. If this is so, then the activation energy for acceleration stress should resemble that for hypoxia stress. From the experimental data of Madden et al[8] on survival of mice to hypoxia of drowning an Arrhenius plot was made, from which the activation energy of survival to hypoxia stress was calculated to be 8.4 kilocalories per mole (Table 1). Since the activation energy of acceleration stress (12-13 kcal/M) is substantially different from that of hypoxia stress (8.4 kcal/M), resistance to acceleration stress must be governed by additional or different mechanisms than those responsible for hypoxia stress.

To provide perspective, let us compare the activation energies of acceleration and hypoxia stress with the activation energy of brain function. We shall use the data of Hoagland[9] on the activation energies of the frequency of the alpha rhythm of the electroencephalogram (EEG). Table 1 shows that the EEG of the undamaged human brain is 8 kilocalories per mole which is approximately the activation energy of the cytochrome oxidase reaction[10]. This resembles the 8.4 kilocalories per mole measured for hypoxia stress, which supports the concept that survival to hypoxia stress is governed by cerebral impairment, which is a prevalent hypothesis due to the well-known sensitivity of the brain to oxygen lack. Humans with moderate brain damage showed an increase in EEG activation energy to 11 kilocalories per mole (Table 1), which resembles the values seen with acceleration stress. This suggests that the limiting factor in acceleration stress is not simply the ability of the brain to endure hypoxia. Instead, inadequate cerebral and/or retinal circulation may

be causing some sort of additional impairment of nervous tissue to produce an effect resembling moderate brain damage.

References

1. Glasstone, S., K. J. Laidler, and H. Eyring. The Theory of Rate Processes, McGraw-Hill Book Co., New York, 1941.

2. Lardy, H. A. (ed). Respiratory Enzymes, Burgess Publishing Co. Minneapolis, 1939.

3. Johnson, F. H., H. Eyring, and M. J. Polissar. The Kinetic Basis of Molecular Biology, John Wiley & Sons, New York, 1954.

4. Morales, M. M. : A note on limiting reactions and temperature coefficients J. Cell. Comp. Physiol. 30: 303-314, 1947.

5. Crozier, W. J. : The distribution of temperature characteristics for biological processes; critical increments for heart rates. J. Gen. Physiol. 9: 531-546, 1926.

6. Stiehm, E. R.: Different effects of hypothermia on two syndromes of positive acceleration. J. Appl. Physiol. 18: 387-392, 1963.

7. Burgess, B. F.: The effect of temperature on tolerance to positive acceleration. Aerospace Med. 30: 567-571, 1959.

8. Maddon, R. F., F. W. Stemler, and W. A. Hiestand: Effect of certain chemical agents and physical conditions on the body temperature of mice and the relationship of temperature to drowning survival. Amer. J. Physiol. 180: 121-123, 1955.

9. Hoagland, H.: Pacemakers in human brain waves in normals and in general paretics. Amer. J. Physiol. 116: 604-615, 1936.

10. Cope, F. W., and K. D. Straub: Calculation and measurement of semicon-

duction activation energy and electron mobility in cytochrome oxidase, with evidence that change carriers are polarons, which may couple oxidation to phosphorylation. Bull. Math. Biophys. 31: 761-774, 1970.

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13. ABSTRACT

The activation energy of 13 kcal/M for loss of peripheral vision in man subjected to acceleration stress of +4 to +5 G_z resembles that of 12 kcal/M for survival of rats of +40 G_z, which suggests that the physiological mechanisms of acceleration protection are similar in the two species The activation energy of survival to hypoxia stress (mouse) is 8.4 kcal/M which resembles the value of 8 kcal/M obtained for function of the normal human brain (alpha frequency of the EEG), which supports the concept that survival of the organism to hypoxia stress is indeed limited by survival of brain function The large difference in activation energy of acceleration stress from that of hypoxia or of normal brain function suggests that tolerance to acceleration stress is not limited simply by the ability of nervous tissue to endure hypoxia, but must be dependent upon additional mechanisms

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